Annex 3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:
DIDEBERG et al. : GROUP ART UNIT: 1645

SERIAL NO: 10/520,655

FILED: July, 11, 2003 : EXAMINER: GANGLE, Brian, J.

FOR: STREPTOCOCCUS PNEUMONIAE PBP2X MINI-TROTEIN AND USE THEREOF

DECLARATION UNDER 37 C.F.R. 1.132

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, D.C.

SIR:

Now comes Thierry VERNET, who declares and states that:

1. I am a graduate of Strasbourg Louis Pasteur University and received my PhD degree in the year 1981

2. I have been employed by COMMISSARIAT A L'ENERGIE ATOMIQUE for 12 years as a researcher in the field of molecular biology

3. I declare that I am experienced in the field of molecular biology and biochemistry as it emerges from the publication list herewith attached.

4. *Written description*:

- The recombinant protein of the invention (named mini-PBP2x) comprises concatenated fragments of a PBP2x protein of *Streptococcus pneumoniae*; the four fragments of said PBP2x protein of *S. pneumoniae* are situated at positions corresponding respectively to positions 74-90, 186-199, 218-228 and 257-750 of PBP2x protein of the strain R6 of *Streptococcus pneumoniae* disclosed in figure 1, and each fragment is preceded by a linking peptide of 1 to 7 amino acids.

- It clearly emerges from the specification that the PBP2x is a well-known protein of *S. pneumoniae*. The encoding gene (*pbpX* gene) has been identified (see page 6, lines 10 to 14) and numerous PBP2x protein sequences from different isolates of *S. pneumoniae* are available in the sequence data bases (see the accession numbers indicated in Annex 1). The structure including the 3D structure, as well as the structure-function relationship of the PBP2x have been determined (page 3, line 7 to page 4, line 3 of the specification).

- The sequence of the PBP2x of other isolates may be obtained by conventional molecular biology techniques, according to standard protocols which are well-known in the art. For example, the nucleic acid sequence encoding the PBP2x protein is amplified by PCR, RT-PCR and/or cloned by screening genomic DNA libraries by hybridization with homologous probe, as specified page 11, lines 26 to 29 of the specification. Primers suitable for the PCR or RT-PCR amplification are disclosed page 11, lines 29 to 31 of the specification and in the sequence listing. Given the sequence conservation of PBP2x as mentioned below, these primers are suitable for amplifying the PBP2x coding sequence from any strain of *S. pneumoniae*.

- The present Application discloses the amino acid sequence of the four fragments of the PBP2x protein of the strain R6 of *S. pneumoniae* and their position relatively to the PBP2x amino acid sequence (figure 1).

- PBP2x sequence alignments (see the results of the sequence comparison in Annex 2) clearly indicates that the PBP2x protein is very conserved (86 % identity). Furthermore, no gaps were found between the different PBP2x sequences (see Annex 2).

- Therefore, the skilled artisan will obtain directly the sequence of the four fragments of the claimed recombinant protein for any PBP2x.

- In addition, the sequence of the linking peptide is specified in the present Application the linking peptide may consist of homologous sequence (*ie* amino acids flanking the fragments in the PBP2x amino acid sequence (see page 5, lines 26 to 32) or heterologous sequences (small amino acids : A, S, G or T; see page 6, lines 3 to 6).

- The recombinant protein of the invention is produced by conventional molecular biology techniques, according to standard protocols which are well-known in the art. For example, the nucleic acid sequence encoding the PBP2x protein is amplified by PCR, RT-PCR and/or cloned by screening genomic DNA libraries by hybridization with homologous probe, as mentioned above in item 3. The recombinant protein is derived from the PBP2x protein by standard mutagenesis techniques. For example, the deletion of the PBP2x sequences and the insertion of the linking peptide may be carried by site-directed mutagenesis on a phagemide, followed by PCR amplification of the mutagenised sequence and cloning in an expression vector, as described for example page 12, lines 1 to 9 and in example 1 of the instant Application.

* * * * *

Thus, as specified hereabove, the claimed recombinant protein comprises four perfectly defined fragments of a protein whose sequence, structure and structure-function relationship are perfectly known, and each fragment is preceded by a linking peptide whose sequence is specified in the instant Application.

For these reasons, the specification provides a written description for the claimed recombinant protein.

5. *Enablement:*

- As it emerges from the hereabove, the specification enables any person skilled in the Art to make and use the invention commensurate in scope with the instant claims.

- In addition to what is specified hereabove as regards the written description, the recombinant protein of the invention (mini-PBP2x) comprises mutations in the non penicillin binding domain (or n-PB: positions 50 to 265); the penicillin–binding domain/transpeptidase domain (positions 266 to 615) which represent the major target for identifying novel antibiotics active on beta-lactam resistant strains of *S. pneumoniae* is intact in the recombinant protein of the invention.

- Furthermore, example 2 which discloses a mini-PBP2x derived from the PBP2x of the strain R6 of *S. pneumoniae*, clearly demonstrates that the enzymatic activity of PBP2x

(binding to beta-lactams and transpeptidase activity) is still present in the mini-PBP2x and equivalent to that of previous PBP2x mutant (PBP2x*) having a deletion of the cytoplasmic and transmembrane domains of PBP2x only (deletions of residues 1 to 48).

- Since, all the PBP2x proteins from different strains of PBP2x are very conserved and share the same structure which correspond to the same function, it is considered that similar results will be obtained with any PBP2x protein.

- Therefore, the results obtained with the mini-PBP2x derived from the strain R6 of *S. pneumoniae* are representative of the functionality of all the recombinant proteins as encompassed by the claims.

- The teaching of the application with the general knowledge at the time the Invention was made, provides the skilled artisan with the information necessary to perform the claimed recombinant protein.

- Thus, the instant claims meet the enablement requirement considering that the Inventors disclose sufficient information for the person skilled in the Art to make and use the full scope of the claimed invention without undue experiments.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the Application or any Patent issued thereon.

June, 21, 2007
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All: 86 Review: 4

Items 1 - 86 of 86 One page.

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Items 1 - 86 of 86

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